Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus

Jonathan I. Silverberg, MD, PhD, MPH,[a] Andreas Pinter, MD,[b] Grazyna Pulka, MD, PhD,[c] Yves Poulin, MD, PhD,[d] Jean-David Bouaziz, MD, PhD,[e] Andreas Wollenberg, MD, PhD,[f] Dédée F. Murrell, MD,[g] Andrew Alexis, MD, MPH,[h] Lisa Lindsey, PhD,[i] Faiz Ahmad, MS,[i] Christophe Piketty, MD, PhD,[j] and Alan Clucas, FRCP, FFPM[k] *Chicago, Ill; Frankfurt am Main and Munich, Germany; Krakow, Poland; Quebec City, Quebec, Canada; Paris and Sophia Antipolis, France; Sydney, Australia; New York, NY; Fort Worth, Tex; and Lausanne, Switzerland*

Background: Nemolizumab targets the IL-31 receptor α subunit involved in atopic dermatitis (AD) pathogenesis.
Objective: We sought to evaluate a new dosing strategy of nemolizumab in patients with AD.
Methods: We performed a 24-week, randomized, double-blind, multicenter study of nemolizumab (10, 30, and 90 mg) subcutaneous injections every 4 weeks versus placebo, with topical corticosteroids in adults with moderate-to-severe AD, severe pruritus, and inadequate control with topical treatment (n = 226). The Eczema Area and Severity Index (EASI), the peak pruritus (PP) numeric rating scale (NRS), and the Investigator's Global Assessment (IGA) were assessed. Standard safety assessments were performed.
Results: Nemolizumab improved EASI, IGA, and/or NRS-itch scores, with the 30-mg dose being most effective. Nemolizumab (30 mg) reduced EASI scores versus placebo at week 24 (−68.8% vs −52.1%, $P = .016$); significant differences were observed by week 8 ($P \leq .01$). With significant improvement ($P = .028$) as early as week 4, IGA 0/1 rates were higher for 30 mg of nemolizumab versus placebo at week 16 (33.3% vs 12.3%, $P = .008$) but not week 24 because of an increased placebo/topical corticosteroid effect (36.8% vs 21.1%, $P = .06$). PP-NRS scores were improved for 30 mg of nemolizumab versus placebo at week 16 (−68.6% vs −34.3%, $P < .0001$) and week 24 (−67.3% vs −35.8%, $P < .0001$), with a difference by week 1 ($P < .001$). NRS response rates (≥4-point decrease) were greater for 30 mg of nemolizumab versus placebo at week 16 ($P \leq .001$) and week 24 ($P \leq .01$). Nemolizumab was safe and well tolerated. The most common adverse events were nasopharyngitis and upper respiratory tract infection.
Conclusions: Nemolizumab resulted in rapid and sustained improvements in cutaneous signs of inflammation and pruritus in patients with AD, with maximal efficacy observed at 30 mg. Nemolizumab had an acceptable safety profile. (J Allergy Clin Immunol 2020;145:173-82.)

Key words: *Atopic dermatitis, humanized mAb, anti–IL-31 receptor*

From [a]the Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago; [b]the Department of Dermatology, Venereology, and Allergology, Goethe-Universität Frankfurt am Main; [c]the School of Medicine, Jagiellonian University Medical College, Krakow; [d]the Department of Medicine, Université Laval, Quebec City; [e]the Department of Dermatology, Paris VII Sorbonne Paris Cité University Assistance Publique–Hôpitaux de Paris; [f]the Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, Munich; [g]the Department of Dermatology, St George Clinical School, University of New South Wales, Sydney; [h]the Department of Dermatology, Icahn School of Medicine, Mount Sinai, New York; [i]Galderma Laboratories, Fort Worth; [j]Galderma R&D, Lausanne; and [k]Retired, Sophia Antipolis.

The study was funded by Nestlé Skin Health-Galderma R&D. The funders participated in the conception and design of the study, analysis and interpretation of the data, and drafting and critical revision of the report and provided approval to submit.

Disclosure of potential conflict of interest: J. I. Silverberg has received honoraria as a speaker/consultant for Galderma, Abbvie, AnaptysBio, Asana, Arena, Boehringer Ingelheim, Dermavant, Eli Lilly, GlaxoSmithKline, Glenmark, Kiniksa, Leo, Menlo, Novartis, Pfizer, Regeneron-Sanofi, and Realm and has received grants as an investigator from Galderma and GlaxoSmithKline. A. Pinter has received compensation as an investigator, speaker, or advisor from AbbVie, Allmirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pfizer, Tigercat Pharma, Regeneron, Roche, Sanofi Aventis, Sandoz Biopharmaceuticals, Schering-Plous, and UCB Pharma. Y. Poulin has received grants as an investigator for Galderma, Abbvie, Amgen, AnaptysBio, Boehringer Ingelheim, Bond Avillion, Celgene, Devonian, Eli Lilly, GlaxoSmithKline, Janssen, Leo Pharma, Merck Serono, Pfizer, and UCB Pharma. A. Wollenberg has received grants, personal fees, and/or nonfinancial support from Almirall, Beiersdorf, Bioderma, Chugai, Galapagos, Galderma, Hans Karrer, Leo Pharma, Eli Lilly, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, Santen, and Sanofi-Aventis. D. F. Murrell has received grants as investigator and honoraria as advisor for Galderma, Sanofi, Anacor, Pfizer, Menlo, Pierre Fabre, and GlaxoSmithKline and has also served as an investigator for Regeneron and Medimmune. A. Alexis has served as an investigator and consultant for Galderma, Leo, Novartis, Almirall, Celgene, and Rxl; as an investigator for Bristol-Myers Squibb, Menlo, and SkinMedica; and as a consultant for Pfizer, Sanofi-Regeneron, Trevi, Dermavent, Unilever, BioPharmX, Cipla, Beiersdorf, Valeant, L'Oreal, and P&G. L. Lindsey, F. Ahmad, C. Piketty, and A. Clucas are or were employees of Galderma at the time of the study. The rest of the authors declare that they have no relevant conflicts of interest.

Clinicaltrials.gov trial registration no. NCT03100344 and EUDRACT no. 2016-005025-37.

Received for publication April 4, 2019; revised July 31, 2019; accepted for publication August 13, 2019.

Available online August 23, 2019.

Corresponding author: Jonathan I. Silverberg, MD, PhD, MPH, 676 N St Clair St #1600, Chicago, IL 60611. E-mail: jonathanisilverberg@gmail.com.

0091-6749

https://doi.org/10.1016/j.jaci.2019.08.013

Abbreviations used
AD: Atopic dermatitis
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index
EASI50: Greater than 50% improvement in EASI score
EASI75: Greater than 75% improvement in EASI score
EASI90: Greater than 90% improvement in EASI score
EQ5D: EuroQoL 5-Dimension
HADS: Hospital Anxiety and Depression Scale
IGA: Investigator's Global Assessment
ITT: Intent to treat
LS: Least square
NRS: Numeric rating scale
PP: Peak pruritis
TCS: Topical corticosteroid
TEAE: Treatment-emergent adverse event

Nemolizumab is a humanized mAb that targets the IL-31 receptor α subunit; it has been formulated for subcutaneous injection and studied in patients with atopic dermatitis (AD).[1-3] IL-31 is a member of the IL-6 family of cytokines, which are central to the progression of chronic disease.[4] Recent information has implicated IL-31 in the pathogenesis of AD.[1,5-10] IL-31 is responsible for a distinct transcriptional program in sensory neurons that causes nerve elongation and branching and might underly the tendency of patients with AD to experience "increased sensitivity to minimal stimuli inducing sustained itch."[11]

Nemolizumab binds to the IL-31 receptor on a spectrum of cells, including neurons, which is potentially its mechanism in relieving pruritus.[2] IL-31 regulates brain-derived natriuretic peptide in dorsal root ganglions and the skin, thereby regulating cytokine and chemokine release and controlling itch signaling pathways.[12] Thus inhibition of IL-31 and its actions on brain-derived natriuretic peptide provides a novel therapeutic approach for AD. From a broader perspective, IL-31 helps drive T_H2-associated inflammation by modulating keratinocyte differentiation and the immune response through stimulation of proinflammatory cytokines.[13] Increased skin barrier penetration of allergens and irritants has been shown to accompany IL-31–associated alteration of keratinocyte differentiation.[13] Furthermore, IL-31 can induce pathologic remodeling of the skin through increased epidermal basal cell proliferation, leading to epidermal thickening, and stimulated transepidermal water loss and additional impaired skin barrier function.[14]

Pruritus is the most burdensome symptom of AD and drives the "itch-scratch cycle," increasing skin barrier damage and resulting in sleeplessness, fatigue, and poor quality of life.[2,15,16] Pruritus can directly impair psychosocial well-being and quality of life, leading to increased stress and depressive symptoms.[17] Topical treatments for AD do not control disease, particularly pruritus, for all patients, and current systemic therapies are associated with long-term safety concerns.[1] There is a core group of patients for whom treatment options are limited and who need new safe and efficacious treatments.[18]

Nemolizumab targets the IL-31 pathway to manage both signs and symptoms of AD. In patients with moderate-to-severe AD, nemolizumab monotherapy (phase 2a study) or combined therapy with topical corticosteroids (TCSs; phase 1 study) was associated with rapid and sustained relief of pruritus and improvement of dermatitis.[1,3] This phase 2b study assessed the efficacy and safety of nemolizumab in combination with TCSs to determine the optimal dose and duration of therapy. TCSs were included because they are commonly used with systemic regimens for AD.[19] Although prior studies of nemolizumab in patients with AD used a weight-based dosage, this study evaluated a more patient-centric dosing strategy, including a loading dose to rapidly achieve steady-state drug concentrations (4 vs 10-12 weeks) and a fixed dose to allow potential use of a convenient autoinjector. This mirrors current development trends with biologic agents. We chose to assess nemolizumab in this more clinically relevant scenario.

The loading dose and flat dose were selected based on the clinical pharmacokinetic profile of nemolizumab. The phase 2a study demonstrated that steady-state concentrations were achieved at week 16 of treatment without a loading dose. Pharmacokinetic models showed that fixed doses of 10, 30, and 90 mg were expected to provide similar systemic exposure levels to those observed in the previous phase 2a study. In addition, loading doses were added (20 mg for the 10-mg dose and 60 mg for the 30-mg dose) to rapidly achieve targeted systemic levels and ensure a fast onset of action.

METHODS

The nemolizumab phase 2b study was conducted in North America (the United States and Canada), Europe (France, Germany, and Poland), and Australia. This clinical study was conducted in accordance with the protocol, the Helsinki declaration (1964) and subsequent amendments, and the International Conference on Harmonization Good Clinical Practice guidelines and in compliance with applicable regulatory requirements.

Study design

This was a double-blind, randomized, placebo-controlled multicenter study of subcutaneous nemolizumab versus placebo. Nemolizumab was administered as a loading dose of 20, 60, or 90 mg on day 1, followed by 10, 30, or 90 mg, respectively, every 4 weeks until week 20 (injections at weeks 4, 8, 12, 16, and 20) and a 12-week follow-up period until week 32. All treatment arms also received background midpotency or low-potency TCSs started at the screening visit in a standardized regimen and moisturizer (either the subject's preferred moisturizer or moisturizer suggested by the investigator).

Patient population

Subjects had moderate-to-severe AD, which was defined as an Investigator's Global Assessment (IGA) score of 3 or 4, and severe AD–associated pruritus uncontrolled by topical treatments. Severe pruritus was defined as a Pruritus Categorical Scale score of severe on at least 3 of the last 7 days before screening and an average daily peak pruritus (PP) numeric rating scale (NRS) intensity of 7 or greater for 7 days before the baseline visit. Additional inclusion criteria were age of 18 years or greater, chronic AD present for 2 or more years, body surface area involvement of 10% or greater, and an Eczema Area and Severity Index (EASI) score of 12 or greater. Patients also had a documented inadequate response to topical treatments within the past 6 months and were currently using TCSs but also agreed to using only authorized TCSs throughout the study and agreed to use a moisturizer at least once per day. Additional criteria and definitions of inadequate response to topical treatments are provided in the supplementary information provided in this article's Online Repository at www.jacionline.org.

Rescue therapy was allowed at any time during the study if deemed medically necessary by the investigator because of significant worsening of signs/symptoms of AD. It could take the form of a greater potency or greater

TABLE I. Patients' demographics and baseline characteristics (ITT population)

	Placebo (n = 57)	Nemolizumab, 10 mg (n = 55)	Nemolizumab, 30 mg (n = 57)	Nemolizumab, 90 mg (n = 57)	Total (n = 226)
Sex					
Male	31 (54.4%)	29 (52.7%)	29 (50.9%)	26 (45.6%)	115 (50.9%)
Female	26 (45.6%)	26 (47.3%)	28 (49.1%)	31 (54.4%)	111 (49.1%)
Race					
White	45 (78.9%)	38 (69.1%)	40 (70.2%)	44 (77.2%)	167 (73.9%)
Black/African American	8 (14.0%)	3 (5.5%)	10 (17.5%)	8 (14.0%)	29 (12.8%)
Asian	4 (7.0%)	11 (20.0%)	6 (10.5%)	4 (7.0%)	25 (11.1%)
Other	0	3 (5.4%)	1 (1.8%)	1 (1.8%)	5 (2.2%)
Ethnicity					
Hispanic/Latino	5 (8.8%)	2 (3.6%)	2 (3.5%)	2 (3.5%)	11 (4.9%)
Non-Hispanic/Latino	52 (91.2%)	53 (96.4%)	55 (96.5%)	55 (96.5%)	215 (95.1%)
Age (y)					
Mean (SD)	40.9 (15.01)	35.3 (14.83)	40.2 (16.64)	40.9 (14.95)	39.3 (15.45)
Range	18-72	18-82	18-80	19-77	18-82
Weight (kg)					
Mean (SD)	80.58 (18.84)	73.72 (14.63)	76.90 (18.61)	80.49 (22.77)	77.96 (19.05)
Mean EASI score (SD)	26.96 (12.44)	24.80 (10.20)	25.87 (10.53)	24.24 (10.41)	25.48 (10.92)
IGA score					
3 (moderate)	38 (66.7%)	37 (67.3%)	39 (68.4%)	37 (64.9%)	151 (66.8%)
4 (severe)	19 (33.3%)	18 (32.7%)	18 (31.6%)	20 (35.1%)	75 (33.2%)
Mean AD involvement of BSA (SD)	45.6 (22.60)	40.4 (15.66)	42.4 (17.10)	37.6 (18.08)	41.5 (18.65)
Weekly PP-NRS score					
Mean ± SD	8.16 ± 1.17	8.62 ± 1.05	8.22 ± 1.39	8.22 ± 1.29	8.30 ± 1.24
Range	3.6-10.0	5.4-10.0	0.6-10.0	2.4-10.0	0.6-10.0
Weekly average pruritus NRS score					
Mean ± SD	7.52 ± 1.52	8.01 ± 1.28	7.62 ± 1.56	7.76 ± 1.39	7.72 ± 1.44
Sleep NRS score	7.7 ± 1.75	8.2 ± 1.27	7.6 ± 1.80	7.9 ± 1.43	NA
Mean ± SD SCORAD score	67.90 ± 12.33	66.02 ± 11.37	67.01 ± 11.43	66.04 ± 11.33	66.74 ± 11.57
Mean DLQI score	17.0 ± 6.60	16.5 ± 6.41	15.6 ± 7.28	16.6 ± 7.36	NA
Mean HADS score	12.2 ± 8.23	14.6 ± 6.79	12.1 ± 7.26	14.0 ± 8.36	NA

Percentages are based on the number of subjects with a nonmissing value in the respective treatment arm.
BSA, Body surface area; *NA*, not available.

quantity of TCSs, use of a topical calcineurin inhibitor, systemic treatment, phototherapy, or combinations of treatments. Study drug was continued unless there was a safety concern or rescue with systemic therapies. Subjects who received rescue therapies were considered treatment failures for the efficacy analysis.

Efficacy and safety assessments

The primary efficacy end point was percentage change from baseline in EASI score at week 24. Secondary end points were the proportion of subjects achieving IGA success (IGA clear [0] or almost clear [1]) at week 24; other assessments at each visit included percentage change in EASI score, the PP-NRS score, and the proportion of subjects with improvement in PP-NRS scores of 4 or greater, sleep disturbance NRS scores, change in SCORAD score, and proportion of subjects achieving EASI score reduction of 50%, 75%, or 90% from baseline at week 24. Standard safety assessments were performed (specific information about additional safety and other assessments is provided in the supplementary information in this article's Online Repository).

Quality of life was assessed by using the Dermatology Life Quality Index (DLQI) and EuroQoL 5-Dimension (EQ5D) scales and the Hospital Anxiety and Depression Scale (HADS). The DLQI is a 10-item questionnaire focusing on how skin disease affects overall life quality; each question is rated on a scale of 0 (not at all) to 3 (very much). EQ5D is a 2-part tool, with a visual analog score and descriptive questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Mental health symptoms were assessed by using HADS. HADS is a 14-item instrument, with 7 questions each for anxiety and depression. Ratings are from 0 to 3, with a total score of 0 to 21 for each subscale.

Statistical analysis

SAS software (version 9.3; SAS Institute, Cary, NC) was used, and statistical analyses were performed on the following subject populations: the intent-to-treat (ITT, all randomized subjects), per-protocol (ITT subjects who met all major protocol criteria), and safety (ITT subjects with ≥1 study drug application) populations. All efficacy variables were summarized by treatment at each visit. Continuous data were summarized by using means, medians, minimum, maximum, and SDs, and categorical variables were summarized by frequency and percentage for each response category. Primary and secondary continuous end points were analyzed by using a mixed-effects model for repeated measures approach, including terms of treatment group and baseline IGA severity. All categorical end points were analyzed by using the stratified Cochran Mantel-Haenszel test, and time-to-event data were summarized and analyzed by using the Kaplan-Meier method. Multiple imputation and last observation carried forward methodologies were used as sensitivity analyses to impute missing values. With binary end points, all missing values were treated as "nonresponders." All efficacy data, except the observed case, were set to missing after rescue medication use. Safety analyses were performed on the safety population. Adverse events were tabulated in frequency tables by using the System Organ Class and MedDRA preferred terms.

RESULTS

Patient population

A total of 226 subjects were included in the ITT analysis, with group sizes shown in Table I; 225 of these were included in the safety population. Subject disposition is provided in the supplementary material in this article's Online Repository. Baseline

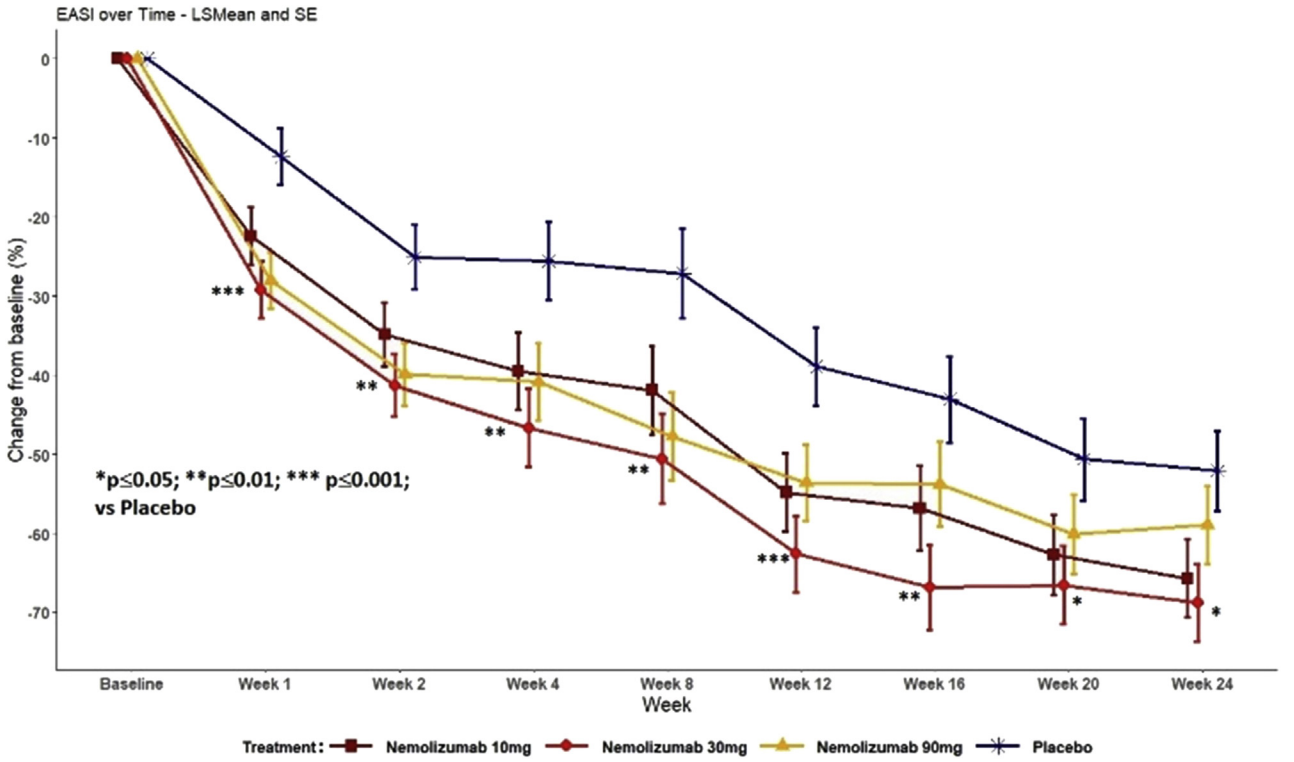

FIG 1. Mean percentage change from baseline in EASI scores over time (ITT population).

demographic and clinical disease characteristics were comparable between groups and are shown in Table I.

Efficacy: AD and inflammation

EASI. All nemolizumab doses showed greater improvement in mean percentage change in EASI score at week 24 than placebo (Fig 1). At week 24, the greatest difference from baseline was seen with the 30-mg nemolizumab dose (−68.8% vs −52.1%, least-square [LS] mean reduction for placebo; $P = .016$). A greater statistically significant difference was observed at week 16 with the 30-mg dose (−66.8% vs −43.1%, $P < .01$).

Proportions of subjects reaching greater than 50% (EASI50), 75% (EASI75), and 90% (EASI90) improvement in EASI score from baseline were also analyzed (Fig 2). There were significantly more responders in all nemolizumab treatment groups at most study visits, with best response rates occurring in the 30-mg dose group. At week 24, EASI50 was achieved in 66.7% versus 43.9% of subjects in the 30-mg nemolizumab versus placebo groups ($P = .014$), EASI75 was achieved in 45.6% versus 26.3% ($P = .034$), and EASI90 was achieved in 29.8% versus 10.5%, respectively ($P = .011$). At week 16, EASI50 was achieved in 59.6% versus 36.8% of subjects in the 30-mg nemolizumab versus placebo groups ($P = .016$), EASI75 was achieved in 49.1% versus 19.3% ($P \leq .001$), and EASI90 was achieved in 33.3% versus 8.8%, respectively ($P = .001$).

IGA success. The proportion of subjects with IGA success over time is shown in Fig 3. Performance in the 30- and 90-mg nemolizumab treatment groups was very similar until week 12, after which the 30-mg nemolizumab dose was superior to the other nemolizumab doses. By week 24, 36.8% of subjects in the 30-mg nemolizumab dose achieved IGA success compared with 21.1% in the placebo group ($P = .06$); at week 16, 33.3% of subjects receiving 30 mg of nemolizumab versus 12.3% of patients receiving placebo achieved IGA success ($P = .008$).

SCORAD. At week 24, all 3 doses improved SCORAD scores compared with placebo, with the greatest difference in the 30-mg nemolizumab group. The LS mean absolute change in SCORAD score at week 24 was −25.0 for the placebo group compared with −34.6 ($P = .016$) for the 10-mg nemolizumab group, −37.8 ($P = .001$) for the 30-mg nemolizumab group, and −32.5 ($P = .058$) for the 90-mg nemolizumab group.

Efficacy: pruritus

The LS mean percentage change in PP-NRS score is presented in Fig 4, *A*. All doses of nemolizumab were associated with a rapid decrease in pruritus scores, with statistically significant differences from placebo starting as early as week 1. By week 2, scores with all nemolizumab doses were greater than those with placebo ($P \leq .001$). The most marked effects on PP scores were seen in the 30-mg nemolizumab arm compared with the placebo arm (−67.3% vs −35.8% at week 24, $P < .001$). The proportion of subjects with improvement in weekly average PP-NRS scores of 4 or greater from baseline was significantly greater in the nemolizumab groups versus the placebo group beginning at week 1, when 17.5% of subjects in the 30-mg nemolizumab dose responded compared with 5.3% in the placebo group (Fig 4, *B*).

Efficacy: Additional parameters

Sleep. The LS mean percentage change in weekly average sleep disturbance NRS score at week 24 was −67.5% with 10 mg of nemolizumab, −74.8% with 30 mg of nemolizumab, and

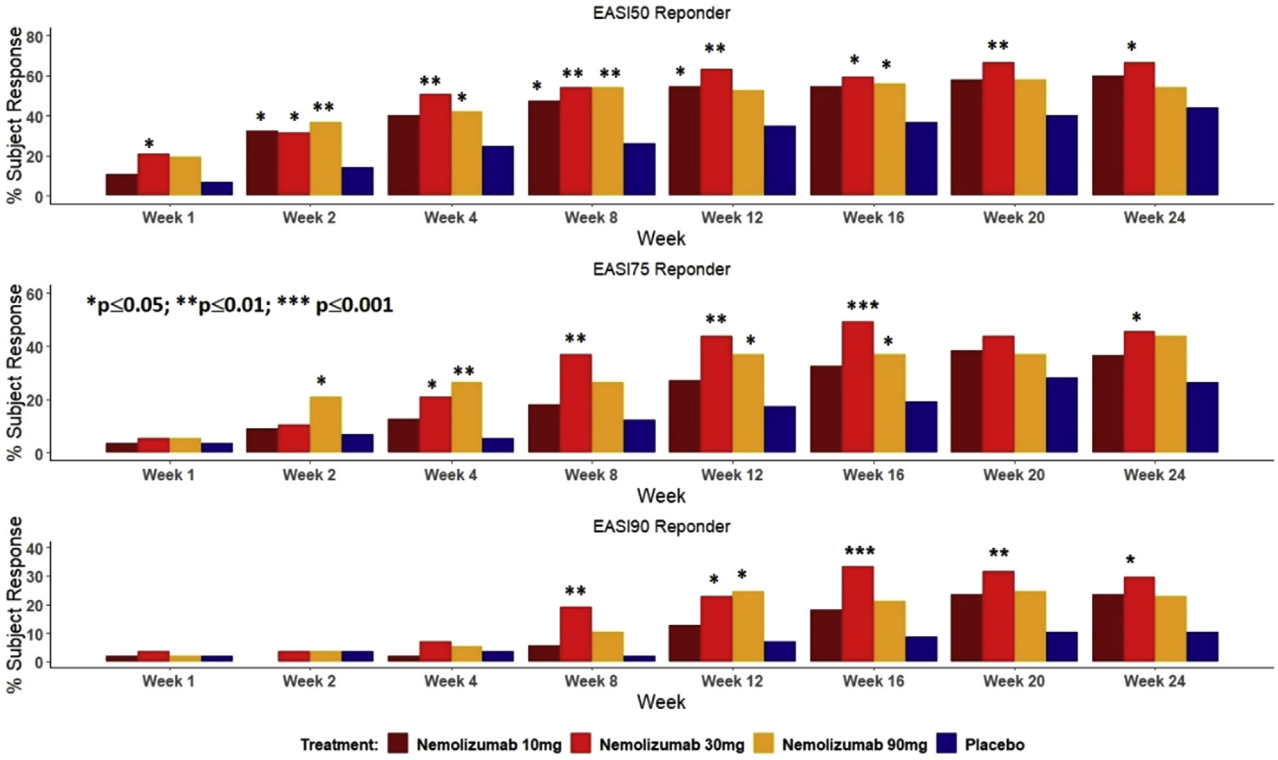

FIG 2. Proportion of EASI 50%, 75%, and 90% responders (ITT population).

−68.1% with 90 mg of nemolizumab compared with −43% with placebo ($P \leq .001$ for all). As shown in Fig 5, a statistically significant difference from placebo was apparent as early as week 1 with all nemolizumab doses.

Quality-of-life assessments. Nemolizumab positively affected quality of life, as assessed by using the DLQI and the visual analog scale section of the EQ5D. DLQI scores decreased significantly in all nemolizumab groups ($P \leq .001$) compared with the placebo group by week 2 and were greater than those in the placebo group at 12 weeks in the 30-mg group ($P = .043$). At week 24, DLQI scores were 4.8 in the 10-mg nemolizumab group (mean, −11.6-point change; $P = .018$), 4.9 in the 30-mg nemolizumab group (mean, −10.5-point change; $P = .022$), and 5.6 in the 90-mg nemolizumab group (mean, −10.9-point change) compared with 8.5 in the placebo group (mean, −8.6-point change). The change from baseline in overall EQ5D index score at week 24 was not significantly different for any nemolizumab group versus the placebo group, although there were positive trends in specific dimensions. Therapy with 30 mg of nemolizumab was associated with significantly superior effects on mobility ($P = .038$), and the 10-mg dose was superior to placebo in mobility ($P = .083$), self-care ($P = .043$), and pain/discomfort ($P = .036$). Changes in visual analog scale scores were significantly different for the 10- and 30-mg doses ($P = .023$ and .047, respectively).

Mental health symptoms. Mean HADS scores were comparable among groups at baseline and by week 24 had decreased by a mean of −7.1 points in the 10-mg nemolizumab group, −4.3 points in the 30-mg nemolizumab group, −4.6 points in the 90-mg nemolizumab group, and −4.2 points in the placebo group. Nemolizumab did not have a significantly different effect on absolute scores on the HADS Anxiety subscale at week 12 or 24. There were significant differences from baseline on the HADS Depression subscale at week 24 in the 10-mg ($P = .007$) and 30-mg ($P = .048$) nemolizumab groups. Similarly, significant differences were not apparent in the group of subjects with HADS Anxiety subscores of 11 or greater or those with HADS Depression subscores of 11 or greater at baseline.

Use of background TCSs. The use of medium- and low-potency TCSs during the treatment period was greater in the placebo group than in all nemolizumab groups at each monthly checkpoint. The total mean use of TCSs from baseline to week 24 was 139.88 g in the 10-mg nemolizumab group, 167.53 g in the 30-mg nemolizumab group, and 163.43 g in the 90-mg nemolizumab group compared with 232.75 g in the placebo group. Note that subjects who received rescue treatment or discontinued the study were excluded from all TCS use analyses. The majority of subjects used medium-potency TCSs, and placebo-treated subjects used almost twice the amount compared with the nemolizumab group. There was a 30% to 40% reduction in TCS use in the nemolizumab groups versus the placebo group.

Use of rescue medication. Rescue medication was required during the treatment period by a total of 34 subjects; 6 in the 10-mg nemolizumab group, 7 in the 30-mg nemolizumab group, 8 in the 90-mg nemolizumab group, and 13 in the placebo group. As shown in Table II, use of both topical and systemic rescue medications were more common in the placebo group compared with the nemolizumab groups.

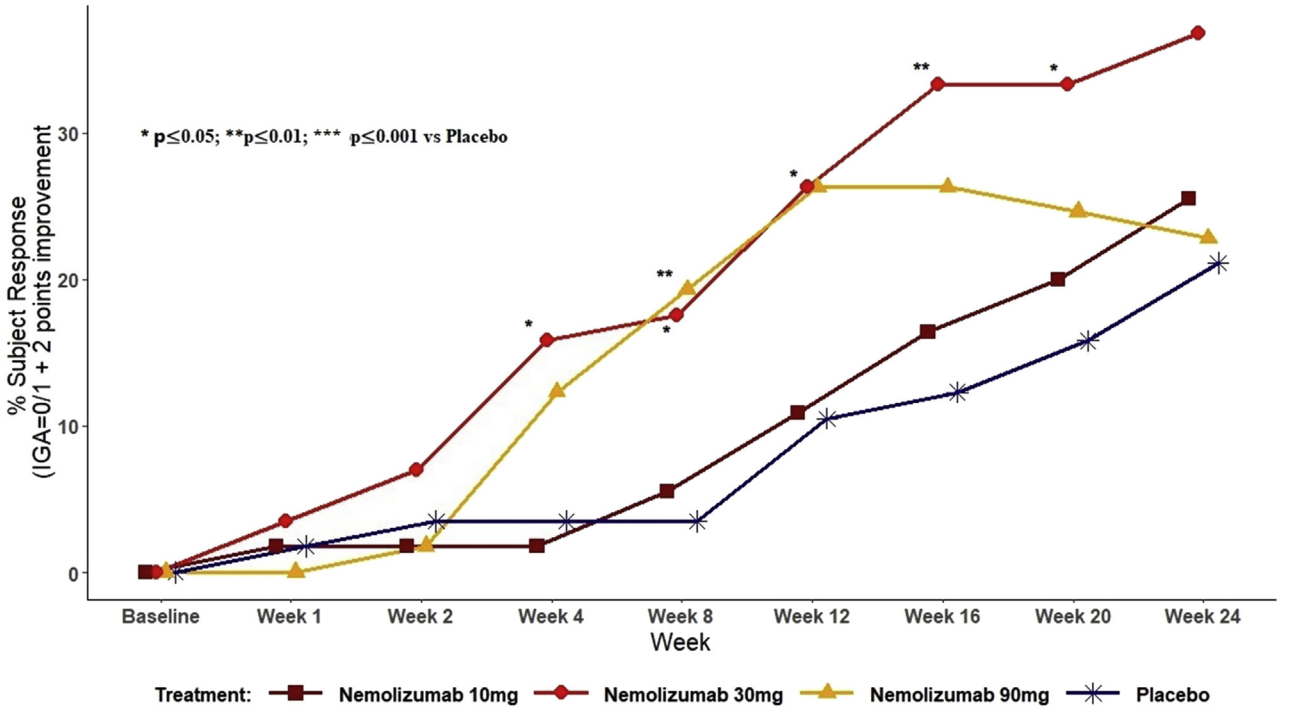

FIG 3. Proportion of subjects achieving IGA success (clear/almost clear plus 2-grade improvement).

Safety

A total of 185 patients had at least 1 adverse event, and the number of treatment-emergent adverse events (TEAEs) was similar in the placebo and all nemolizumab groups. Nemolizumab at all doses was well tolerated, with few serious or severe adverse events; serious TEAEs were reported in 3 (5.5%) of the subjects receiving 10 mg of nemolizumab, 2 (3.5%) subjects in each of the 30- and 90-mg nemolizumab arms, and 1 (1.8%) placebo-treated subject. Severe TEAEs occurred in 6 (10.7%) subjects of the placebo group, 3 (5.5%) subjects of the 10-mg nemolizumab group, 5 (8.8%) subjects of the 30-mg nemolizumab group, and 2 (3.5%) subjects of the 90-mg nemolizumab group.

There were few adverse events leading to discontinuation (2 in the 30-mg group, 4 in the 10-mg group, and 7 in the 90-mg group vs 4 in the placebo group). A summary of the TEAEs occurring in 5% or more subjects is shown in Table III. Selected TEAEs of interest are shown in Table IV.

In subjects with a history of asthma, a greater incidence of asthma events was observed with nemolizumab in a dose-dependent fashion. All asthma events were mostly mild in severity, and there were no *de novo* cases of asthma associated with nemolizumab. One severe event was observed in the 90-mg nemolizumab arm. All events were reversible under treatment. There was a low incidence of peripheral edema observed in both placebo-treated (n = 2, 3.6%) and nemolizumab-treated (n = 8, 4.7%) patients, with no serious cases. Overall, occurrence of the selected TEAEs of interest was acceptable and comparable in the nemolizumab and placebo groups.

Clinical laboratory data showed no significant changes in liver enzymes (alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, or alkaline phosphatase) through week 24. However, 2 subjects treated with nemolizumab (one in the 10-mg arm and the other in the 90-mg arm) discontinued early because of increased creatine kinase levels. There were no signals of effect on C-reactive protein, electrolyte, cholesterol, or glucose levels.

DISCUSSION

This study demonstrated that treatment with nemolizumab resulted in rapid improvement in AD lesions, as assessed by EASI and IGA scores, when compared with placebo. In addition to improvements in inflammatory signs of AD, all assessments of pruritus showed a highly significant, fast-onset, and sustained effect of nemolizumab. The primary end point, percentage change in EASI score at week 24, was statistically significant versus placebo for the 30-mg nemolizumab dose ($P = .016$) and borderline statistically significant for the 10-mg dose ($P = .051$). Although effects on itch and skin lesions have a separate timeline, data from this study clearly demonstrate a reduction in skin lesions and a greater improvement in pruritus. All doses except the 90-mg dose showed improvements in IGA response rates to week 24. Response after week 16 does not appear to increase but remained within expected variability. A similar observation can be made for the 90-mg dose with slightly greater variability, which is likely due to a greater rate of missing responses in this group. The data from this study did not demonstrate a significant dose-response relationship between the 10- and 90-mg doses for clinical efficacy end points; this has been observed with other recent drug candidates, most recently with omalizumab.[20-23] Therefore the dose-response profile of the phase 2b study was further

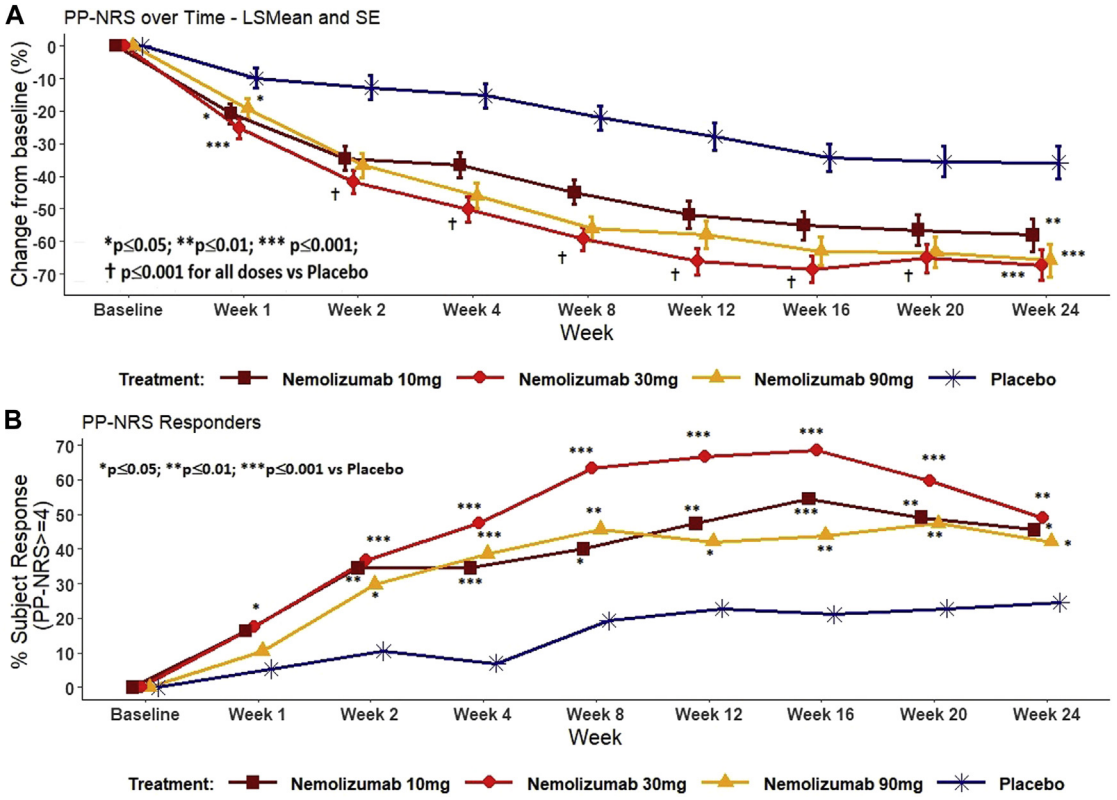

FIG 4. **A,** LS mean percentage change in PP-NRS scores from baseline to week 24 (ITT population). **B,** Proportion of subjects with an improvement of weekly average PP-NRS scores of 4 or greater (ITT population). Any subjects with missing visit or rescue dosing were treated as nonresponders.

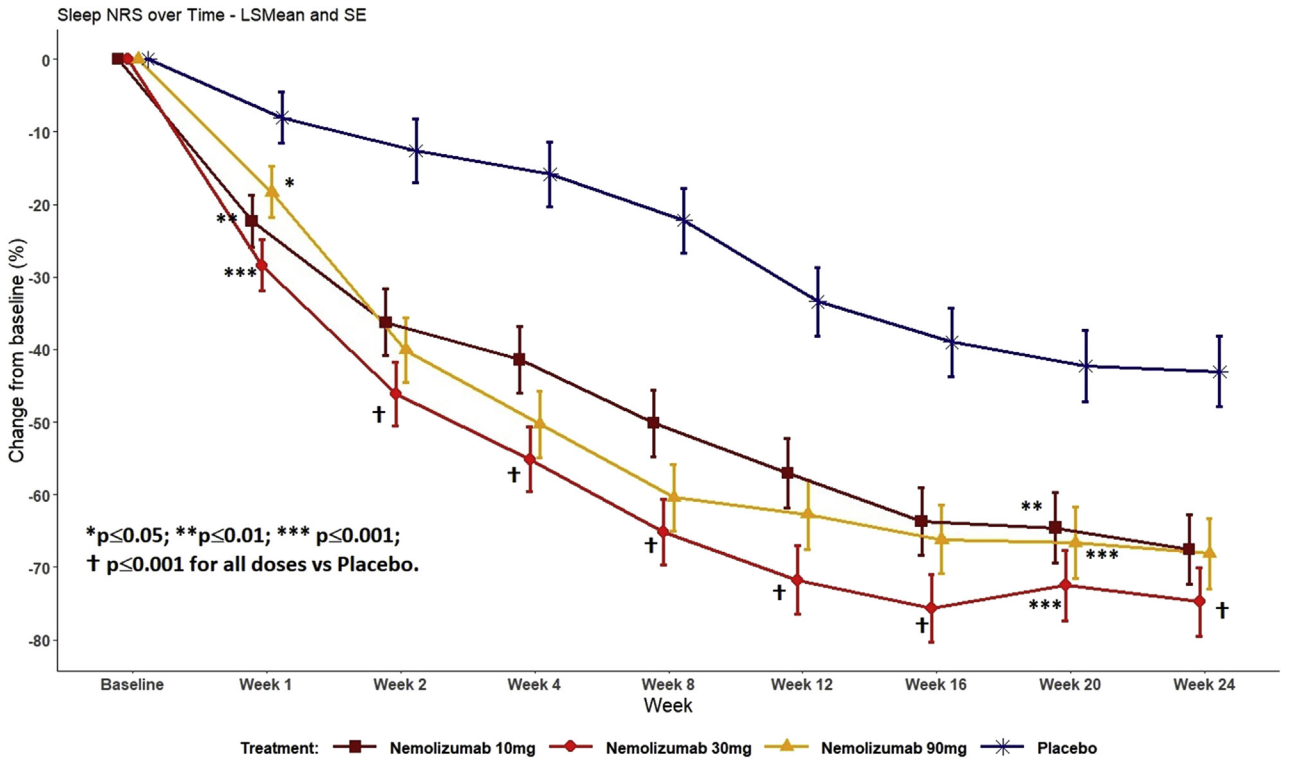

FIG 5. Change in sleep NRS scores over time.

TABLE II. Rescue medication use (ITT population)

	Placebo (n = 57)	Nemolizumab, 10 mg (n = 55)	Nemolizumab, 30 mg (n = 55)	Nemolizumab, 90 mg (n = 55)	Total (n = 226)
Subjects with ≥1 rescue medication and/or procedure					
During treatment period	13 (22.8%*)	6 (10.9%)	7 (12.3%)	7 (14.0%)	34 (15.0%)
During follow-up period	4 (7.0%)	4 (7.3%)	5 (8.8%)	6 (10.5%)	19 (8.4%)
Topical rescue medication (no.)	23	10	9	8	50
Systemic rescue medication (no.)	7	3	1	2	13

The treatment period is defined as from the date of randomization to the date of week 24 (for completers) or 4 weeks after the last study drug injection (for subjects who discontinued the study drug early). The follow-up period is defined as from the date of week 24 (for completers) or 4 weeks after the last study drug injection (for subjects who discontinued study drug early) to the date of week 32/the final visit. Rescue medication data are for the treatment period only.
*Percentage of all rescue medication (topical and systemic).

TABLE III. TEAEs occurring in 5% or greater by system organ class and preferred term, all causes (safety population)

		Nemolizumab			
	Placebo (n = 56)	10 mg (n = 55)	30 mg (n = 57)	90 mg (n = 57)	All (n = 169)
≥1 TEAE	43 (76.8%)	47 (85.5%)	47 (82.5%)	48 (84.2%)	142 (84%)
Infection and infestation	23 (41.4%)	34 (61.8%)	34 (59.6%)	34 (59.6)	102 (60.4%)
Nasopharyngitis	12 (21.4%)	18 (32.7%)	14 (24.6%)	13 (22.8%)	45 (26.6%)
URTI	1 (1.8%)	4 (7.3%)	6 (10.5%)	4 (7%)	14 (8.3%)
Gastroenteritis	0	0	3 (5.3%)	4 (7%)	7 (4.1%)
Sinusitis	0	3 (5.5%)	3 (5.3%)	1 (1.8%)	7 (4.1%)
Oral herpes	1 (1.8%)	2 (3.6%)	1 (1.8%)	3 (5.3%)	6 (3.6%)
UTI	3 (5.4%)	3 (5.5%)	1 (1.8%)	2 (3.5%)	6 (3.6%)
Rhinitis	3 (5.4%)	0	3 (5.3%)	1 (1.8%)	4 (2.4%)
Herpes infection	5 (8.9%)	4 (7.3%)	3 (5.3%)	5 (8.7%)	12 (7.1%)
Skin and subcutaneous tissue disorders	20 (35.7%)	18 (32.7%)	23 (40.4%)	23 (40.4%)	64 (37.9%)
Atopic dermatitis	18 (32.1%)	12 (21.8%)	14 (24.6%)	16 (28.1%)	42 (24.9%)
Dry skin	0	0	3 (5.3%)	0	3 (1.8%)
Respiratory, thoracic, and mediastinal disorders	7 (12.5%)	6 (10.9%)	13 (22.8%)	12 (21.1%)	31 (18.3%)
Asthma event	1 (1.8%)	2 (3.6%)	7 (12.3%)	10 (17.5%)	19 (11.2%)
Cough	2 (3.6%)	1 (1.8%)	3 (5.3%)	2 (3.5%)	6 (3.6%)

UTI, Urinary tract infection; *URTI*, upper respiratory tract infection.

investigated by using pharmacokinetic-pharmacodynamic models. The dose-response fit with an maximum response (E_{max}) or maximum inhibition (I_{max} model), and the maximum nemolizumab effect was observed at serum concentrations close to the observed serum concentration for the 30-mg dose (data not shown).

Week 16 data are presented to facilitate comparisons with the majority of AD studies; however, the week 24 end point was important to better illustrate how nemolizumab performs over a longer period of time. There was also statistically significant separation from placebo in secondary end points, including IGA response, EASI50, EASI75, EASI90, PP-NRS, sleep NRS, and multiple quality-of-life domains, with the greatest differences seen at week 16 and with the 30-mg dose showing superior results to the 3 doses (10, 30, and 90 mg) tested. Further studies will use week 16 as the primary end point, which is consistent with most other clinical trials of new therapies in patients with AD.

The efficacy shown in this study was greater than the results found in the nemolizumab phase 2a study at 12 weeks, particularly with the 30-mg dose. The phase 2a study was a study of nemolizumab monotherapy administered on a weight-based dosing schedule versus placebo.[2] The current data bring new information about the efficacy of nemolizumab in AD with use of a fixed dose of nemolizumab plus a loading dose at baseline, for a longer duration, and in combination with background (low-potency and midpotency) TCSs. Rapid inhibition of pruritus in patients with AD is an important treatment goal. Pruritus relief is expected to contribute to breaking the "itch-scratch cycle" and thus improve the skin condition in patients with AD. In the nemolizumab phase 2b study, steady-state condition was achieved by week 4 because of loading doses of 20 and 60 mg administered in the 10- and 30-mg study arms, respectively. For the 90-mg arm, steady state was reached at approximately week 16 of treatment, which is in full accordance with phase 2a results. It is our opinion that the use of a loading dose to achieve a more rapid steady state and a fixed dose improved the effects of nemolizumab on the inflammatory aspects of AD while retaining the expeditious reduction in patients with pruritus seen in earlier studies. There was a relatively high response rate in the placebo arm, which mirrors the normal TCS response; we believe that this is not a confounder for the study but rather would more closely mimic usual clinical practice should nemolizumab be approved in the management of AD. The study population in the trial represents a difficult-to-treat population in patients with AD; these patients are in need of new therapeutic options. Given the pivotal role of IL-31, it was hypothesized that patients

TABLE IV. Selected TEAEs (safety population)

	Placebo (n = 56)	Nemolizumab, 10 mg (n = 55)	Nemolizumab, 30 mg (n = 55)	Nemolizumab, 90 mg (n = 55)	All nemolizumab groups (n = 169)
No. of selected TEAE	74	75	77	74	226
Subjects with selected TEAEs	31 (55.4%)	37 (67.3%)	37 (64.9%)	37 (64.9%)	112 (66.3%)
AD exacerbation	9 (16.1%)	3 (5.5%)	7 (12.3%)	7 (12.3%)	17 (10.1%)
Injection-related reaction	5 (8.9%)	1 (1.8%)	2 (3.5%)	2 (3.5%)	5 (3%)
Local	3 (5.4%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	3 (1.8%)
Systemic	2 (3.6%)	1 (1.8%)	0	1 (1.8%)	2 (1.2%)
Peripheral edema	2 (3.6%)	2 (3.6%)	4 (7.0%)	2 (3.5%)	8 (4.7%)
Skin infection	7 (12.5%)	7 (12.7%)	9 (15.8%)	6 (10.5%)	22 (13%)
Nonskin infection	21 (37.5%)	31 (56.4%)	31 (54.4%)	31 (54.4%)	93 (55%)
Headache	7 (12.5%)	6 (10.9%)	4 (7.0%)	4 (7.0%)	14 (8.3%)
Subjects with selected serious TEAEs	0	1 (1.8%)	2 (3.5%)	2 (3.5%)	5 (3.0%)
Serious AD exacerbation	0	0	1 (1.8%)	0	1 (0.6%)

with more severe itch would derive greatest benefit. This was incorporated into the study design to more closely mimic clinical realities.

There was a slightly greater incidence of TEAEs and serious TEAEs with nemolizumab compared with placebo. There was no imbalance in the incidence of skin infections between the active and placebo groups, but there was a greater incidence of nonskin infections with nemolizumab versus placebo. Notably, these infections were primarily nasopharyngitis, upper respiratory tract infections, and gastroenteritis. A dose-dependent increase in asthma events in patients with pre-existing asthma was reported, with mostly mild and very few moderate events that were manageable and reversible. All events were observed in subjects with pre-existing asthma, and treatment was adjusted to the course of the disease; most of the cases were mild, with peak expiratory flow decreased in 13 of 24 cases. Some of these events might have occurred because effective treatment with nemolizumab led to improved overall well-being and increased activity levels that, in turn, triggered asthma symptoms. Some of the cases of worsening might have been caused by respiratory tract infections, and it is reassuring that there were no *de novo* cases of asthma associated with nemolizumab. This safety profile is consistent with that reported by Ruzicka et al,[2] except that exacerbation of AD occurred more frequently in the placebo group in our study, whereas it occurred more often in the nemolizumab groups in the earlier study. In addition, greater rates of peripheral edema in the nemolizumab groups[2] were not found in this study.

Study limitations include a small sample size because it was a phase 2b study. This makes it difficult to interpret some of the rare safety events.

In conclusion, of the 3 doses evaluated, the 30-mg every 4-week dose of nemolizumab was the most effective and was associated with the greatest overall efficacy on AD clinical signs and pruritus. Treatment with nemolizumab achieved fast onset and sustained effect on pruritus. Nemolizumab had an acceptable safety profile.

We thank the Nemolizumab Study Team and all investigators in Europe, North America, and Australia (listed in the supplementary section in this article's Online Repository) who participated in this clinical trial, as well as colleagues in Galderma International, Galderma R&D in Sophia Antipolis, and Galderma Laboratories. We also acknowledge the writing support of Valerie Sanders of Sanders Medical Writing in the United States.

Key messages

- **There are patients with moderate-to-severe AD refractory to topical therapies who have limited treatment options.**
- **Nemolizumab is a humanized mAb to the IL-31 receptor α.**
- **IL-31 has broad actions as a proinflammatory and immunomodulatory cytokine, linking the immune and neural systems to induce pruritus in patients with AD.**
- **Nemolizumab monotherapy is effective in patients with AD, with a notable marked rapid effect on pruritus and an acceptable safety profile.**
- **This placebo-controlled, double-blind study evaluated nemolizumab with concomitant use of TCSs in patients with moderate-to-severe AD and severe pruritus.**
- **Nemolizumab had a significant and clinically relevant effect on cutaneous signs of AD compared with placebo, as assessed based on EASI and IGA scores, with a rapid and sustained effect on pruritus.**
- **This study provides confirmation of the importance of IL-31 inhibitors in the management of AD.**

REFERENCES

1. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, et al. Nemolizumab in patients with moderate-to-severe atopic dermatitis: randomized, phase II, long-term extension study. J Allergy Clin Immunol 2018;142:1121-30.e7.
2. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. N Engl J Med 2017;376:826-35.
3. Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. Br J Dermatol 2016;174:296-304.
4. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol 2018;18:773-89.
5. Bilsborough J, Leung DY, Maurer M, Howell M, Boguniewicz M, Yao L, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. J Allergy Clin Immunol 2006;117:418-25.
6. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: involvement of TRPV1 and TRPA1. J Allergy Clin Immunol 2014;133:448-60.

7. Kato A, Fujii E, Watanabe T, Takashima Y, Matsushita H, Furuhashi T, et al. Distribution of IL-31 and its receptor expressing cells in skin of atopic dermatitis. J Dermatol Sci 2014;74:229-35.
8. Nobbe S, Dziunycz P, Muhleisen B, Bilsborough J, Dillon SR, French LE, et al. IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. Acta Dermatovenereol 2012;92:24-8.
9. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 2006;117:411-7.
10. Szegedi K, Kremer AE, Kezic S, Teunissen MB, Bos JD, Luiten RM, et al. Increased frequencies of IL-31-producing T cells are found in chronic atopic dermatitis skin. Exp Dermatol 2012;21:431-6.
11. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. J Allergy Clin Immunol 2016;138:500-8.e24.
12. Meng J, Moriyama M, Feld M, Buddenkotte J, Buhl T, Szollosi A, et al. New mechanism underlying IL-31-induced atopic dermatitis. J Allergy Clin Immunol 2018;141:1677-89.e8.
13. Bagci IS, Ruzicka T. IL-31: a new key player in dermatology and beyond. J Allergy Clin Immunol 2018;141:858-66.
14. Singh B, Jegga AG, Shanmukhappa KS, Edukulla R, Khurana Hershey GH, Medvedovic M, et al. IL-31-driven skin remodeling involves epidermal cell proliferation and thickening that lead to impaired skin-barrier function. PLoS One 2016;11:e0161877.
15. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. J Invest Dermatol 2015;135:56-66.
16. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. Ann Allergy Asthma Immunol 2018;121:340-7.
17. Chrostowska-Plak D, Reich A, Szepietowski JC. Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol 2013;27:e239-42.
18. Silverberg JI. Atopic dermatitis treatment: current state of the art and emerging therapies. Allergy Asthma Proc 2017;38:243-9.
19. Armstrong AW, Huang A, Wang L, Miao R, Patel MY, Gadkari A, et al. Real-world utilization patterns of systemic immunosuppressants among US adult patients with atopic dermatitis. PLoS One 2019;14:e0210517.
20. Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet 2014;384:309-18.
21. Fontenot E, Rossi E, Mumper R, Snyder S, Siamakpour-Reihani S, Ma P, et al. A novel monoclonal antibody to secreted frizzled-related protein 2 inhibits tumor growth. Mol Cancer Ther 2013;12:685-95.
22. Vermeire S, Sandborn WJ, Danese S, Hebuterne X, Salzberg BA, Klopocka M, et al. Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2017;390:135-44.
23. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J Allergy Clin Immunol 2011;128:567-73.e1.